PATENT SPECIFICATION

NO DRAWINGS

881,894

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International Classification:—C07c, d.

COMPLETE SPECIFICATION

Tetrahydropyridine Derivatives

I, PAUL ADRIAAN JAN JANSSEN, of Antwerpse Steenweg 16[1], Vosselaar near Turnhout, Belgium, A Citizen of Belgium, do hereby declare the invention, for which

SPECIFICATION NO. 881,894

By a direction given under Section 17(1) of the Patents Act 1949 this application proceeded in the name of N.V. Research Laboratorium Dr. C. Janssen, a Belgium Limited Liability Company, of Turnhoutse Baan 30, Beerse, Turnhout, Belgium.

THE PATENT OFFICE. DS 61433/1(7)/R.153 200 2/62 PL

salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride,

phenyl radical, an alkoxyphenyl radical containing less than eleven carbon atoms, or a dimethoxyphenyl, hydroxyphenyl, thienyl, trifluoromethylphenyl or monocyclic aromatic hydrocarbon radical containing less than eleven carbon atoms and Alk is an alkylene radical containing from three to six carbon atoms.

The halophenyl radicals may be fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl radicals and the monocyclic aromatic hydrocarbon radicals containing less than eleven carbon atoms may be phenyl, tolyl, xylyl, ethylphenyl, propylphenyl or butylphenyl radicals. The radical Alk may be a butylene, propylene, trimethylene or tetramethylene radical but is preferably a trimethylene radical.

The organic bases of this invention form pharmaceutically acceptable non-toxic salts with a variety of inorganic and strong organic acids including sulphuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic and ascorbic acids. They also form quaternary ammonium

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as an aromatic hydrocarbon, e.g. toluene, xylene; a lower alkanol, e.g. ethanol, butanol; or a lower alkanone, e.g. acetone, butanone, pentanone; and ethers such as dioxane. The reaction may be usefully accelerated by the use of elevated temperatures.

Alternatively, the compounds of the invention can be prepared by reacting an appropriately selected ω - (4 - aryl - 1,2,3,6 - tetrahydropyridine)alkanonitrile with an aryl magnesium halide, decomposing the resulting complex and recovering the product. The ω - (4 - aryl - 1,2,3,6 - tetrahydropyridine)-alkanonitrile required for this synthesis can be prepared by condensing an ω-haloalkanonitrile with an appropriately selected 4 - aryl - 1,2,3,6 - tetrahydropyridine.

The aroylalkyl halides used as intermediates can be prepared conveniently by the Friedel-Crafts reaction employing, for example, γ-chlorobutyryl chloride and benzene or an appropriately substituted benzene such as toluene and xylene, a halogenated benzene such as chlorobenzene, bromobenzene, and

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International Classification:—C07c, d.

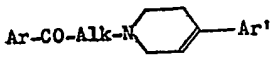
COMPLETE SPECIFICATION

Tetrahydropyridine Derivatives

I, PAUL ADRIAAN JAN JANSSEN, of Antwerpse Steenweg 16[1], Vosselaar near Turnhout, Belgium, A Citizen of Belgium, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to tetrahydropyridine derivatives.

The novel compounds of this invention are 1 - aroylalkyl - 4 - aryl - 1,2,3,6 - tetrahydropyridines of the general formula



and their pharmaceutically useful non-toxic salts wherein Ar and Ar[1] are each a halophenyl radical, an alkoxyphenyl radical containing less than eleven carbon atoms, or a dimethoxyphenyl, hydroxyphenyl, thienyl, trifluoromethylphenyl or monocyclic aromatic hydrocarbon radical containing less than eleven carbon atoms and Alk is an alkylene radical containing from three to six carbon atoms.

The halophenyl radicals may be fluorophenyl, chlorophenyl, bromophenyl, or iodophenyl radicals and the monocyclic aromatic hydrocarbon radicals containing less than eleven carbon atoms may be phenyl, tolyl, xylyl, ethylphenyl, propylphenyl or butylphenyl radicals. The radical Alk may be a butylene, propylene, trimethylene or tetramethylene radical but is preferably a trimethylene radical.

The organic bases of this invention form pharmaceutically acceptable non-toxic salts with a variety of inorganic and strong organic acids including sulphuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulphamic, citric, lactic, maleic, malic, succinic, tartaric, cinnamic, acetic, benzoic, gluconic and ascorbic acids. They also form quaternary ammonium salts with a variety of organic esters of sulphuric, hydrohalic and aromatic sulphonic acids. Among such esters are methyl chloride and bromide, ethyl chloride, propyl chloride, butyl chloride, isobutyl chloride, benzyl chloride and bromide, phenethyl bromide, naphthylmethyl chloride, dimethyl sulphate, diethyl sulphate, methyl benzenesulphonate, ethyl toluenesulphonate, ethylene chlorohydrin, propylene chlorohydrin, allyl bromide, methallyl bromide and crotyl bromide.

The compounds of the invention can be prepared by condensing an aroylalkyl halide of the general formula

Ar—CO—Alk—Halogen

with at least one equivalent of an appropriately selected 4 - aryl - 1,2,3,6 - tetrahydropyridine, where Ar is defined as above. The reaction can be carried out in an inert solvent such as an aromatic hydrocarbon, e.g. toluene, xylene; a lower alkanol, e.g. ethanol, butanol; or a lower alkanone, e.g. acetone, butanone, pentanone; and ethers such as dioxane. The reaction may be usefully accelerated by the use of elevated temperatures.

Alternatively, the compounds of the invention can be prepared by reacting an appropriately selected ω - (4 - aryl - 1,2,3,6 - tetrahydropyridine)alkanonitrile with an aryl magnesium halide, decomposing the resulting complex and recovering the product. The ω - (4 - aryl - 1,2,3,6 - tetrahydropyridine)-alkanonitrile required for this synthesis can be prepared by condensing an ω-haloalkanonitrile with an appropriately selected 4 - aryl - 1,2,3,6 - tetrahydropyridine.

The aroylalkyl halides used as intermediates can be prepared conveniently by the Friedel-Crafts reaction employing, for example, γ-chlorobutyryl chloride and benzene or an appropriately substituted benzene such as toluene and xylene, a halogenated benzene such as chlorobenzene, bromobenzene, and

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fluorobenzene, or an alkoxybenzene such as anisole and phenetole, or thiophene.

These intermediates can also be prepared by treating an ω-haloalkononitrile with the appropriate arylmagnesium bromide followed by acid hydrolysis of the adduct.

The 4 - aryl - 1,2,3,6 - tetrahydropyridines can be prepared according to the method of Schmidle by the condensation of α-methylstyrene, or an appropriate nuclearly substituted derivative thereof, with ammonia and formaldehyde to produce the corresponding 6 - methyl - 6 - aryltetrahydro - 1,3 - oxazine. The acid hydrolysis of the 6 - methyl - 6 - aryl - tetrahydro - 1,3 - oxazine yields the corresponding 4 - aryl - 1,2,3,6 - tetrahydropyridine.

The compounds of the invention have useful pharmacological properties. They are potent anticonvulsants. They are also depressants of the central nervous system and exhibit marked transquilising effects in low dosage. They are also antipyretic, hypnotic and analgesic agents.

The compounds which constitute this invention and the processes for their preparation will appear more fully from a consideration of the following Examples. In these Examples quantities are indicated as parts by weight. Temperatures are expressed in degrees Centigrade (°C.), and pressures are expressed in millimetres of mercury (mm.).

PREPARATION A

A solution of 71 parts of γ-chlorobutyryl chloride and 63 parts of benzene was added with stirring and cooling to a suspension of 71 parts of aluminium chloride in 310 parts of benzene. After the addition was completed, the cooling bath was removed, and the stirring was continued for 30 minutes. The reaction mixture was poured into ice water. The benzene layer was separated, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure to remove the benzene and the residue was distilled to yield γ-chlorobutyrophenone boiling at 134—137°C. at 5 mm. pressure

PREPARATION B

To a suspension of 341 parts of aluminium chloride in 1740 parts of carbon disulphide were added 96 parts of fluorobenzene with stirring and cooling. While the temperature was maintained at about 10°C., 141 parts of γ-chlorobutyryl chloride were added. After the addition was completed, the cooling bath was removed and the stirring was continued for 2 hours. The reaction mixture was then poured into ice water. The organic layer was separated, washed with water, dried over anhydrous sodium sulphate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was distilled to yield γ - chloro - *p* - fluorobutyrophenone boiling at 136—142°C. at 6 mm. pressure.

PREPARATION C

A solution of 95 parts of cold methyl bromide in 356 parts of ether was added portionwise to a suspension of 24 parts of magnesium in 214 parts of ether. The mixture was refluxed for 2 hours. In the course of 90 minutes, 117.5 parts of *p* - tertiary - butylacetophenone were added. The refluxing was continued for 3 hours. The mixture was stirred at room temperature for about 24 hours. The Grignard complex was destroyed by the addition of ammonium chloride and 10% hydrochloric acid solution. The mixture was extracted with ether. The ether extracts were washed with 10% sulphuric acid solution and then with water, dried over anhydrous calcium chloride, and filtered. The solution was concentrated *in vacuo* to remove the solvent. About 0.5 part of hydroquinone was added to the residue which was then heated to a temperature of 100—110°C. under 30 mm. pressure. The distillate was extracted with ether. The extracts were dried over anhydrous calcium chloride and filtered. A small quantity of hydroquinone was added to the solution which was fractionated by distillation to yield - *p* - tertiary - butyl - α - methylstyrene boiling at 98°C. at 5 mm. pressure.

PREPARATION D

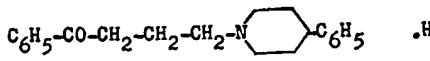
A mixture of 856 parts of ammonium chloride and 3000 parts of 36% formaldehyde solution was stirred and heated to 60°C., 944 parts of α-methylstyrene were added slowly with cooling to maintain this temperature. After the addition was completed, the mixture was stirred at room temperature until the temperature of the reaction mixture dropped to about 40°C. After 2000 parts of methanol were added, the stirring was continued for 20 hours. The methanol was removed *in vacuo*, and the residue was diluted with 2500 parts of concentrated hydrochloric acid. The mixture was then heated with stirring to a temperature of 100°C. for 4 hours, cooled, diluted with 2000 parts of water, and made alkaline by the addition of 15 normal sodium hydroxide solution. The reaction mixture was then extracted with benzene. The benzene extracts were dried over anhydrous potassium carbonate and filtered. The benzene was removed from the filtrate, and the residue was distilled *in vacuo* to yield 4 - phenyl - 1,2,3,6 - tetrahydropyridine boiling at about 97—112°C. at 1 mm. pressure.

This base was dissolved in benzene and dry hydrogen chloride gas was passed through the solution. The precipitated hydrochloride was collected on a filter. The 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melted at about 199—202°C.

EXAMPLE 1

A mixture of 15 parts of γ-chlorobutyrophenone, 24 parts of 4 - phenyl - 1,2,3,6 - tetrahydropyridine, and 0.1 part of potassium iodide in 100 parts of toluene was heated

at a temperature of 100—110°C. The reaction mixture was cooled and then filtered. The residue was extracted with a mixture of 100 parts and water and 100 parts of ether. The ether layer was separated and added to the filtrate from the original reaction mixture. The combined solutions were dried over anhydrous potassium carbonate and filtered. Dry, gaseous hydrogen chloride was introduced into the solution. The precipitate thus obtained was collected on a filter and recrystallised from a mixture of 2-propanol and acetone. In this manner there was obtained 1 - (γ - benzoylpropyl) - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 195—196.2°C. The structural formula was



Substitution of 16.2 parts of 6-chloropentanophenone for the γ-chlorobutyrophenone in the foregoing procedure yielded 1 - (δ - benzoylbutyl) - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride.

EXAMPLE 2

Substitution of an equimolecular amount of *p*-fluoroacetophenone for the *p*-tertiarybutylacetophenone in Preparation C yielded *p* - fluoro - α - methylstyrene boiling at about 93—94°C. at 80 mm. pressure.

Substitution of an equimolecular amount of *p* - fluoro - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (p - fluorophenyl) - 1,2,3,6 - tetrahydropyridine boiling at about 139—141°C. at 4 mm. pressure.

Substitution of 26.7 parts of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*p* - fluorophenyl) 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 182.6—183.6°C.

EXAMPLE 3

Substitution of an equimolecular amount of *p*-chloroacetophenone for the *p*-tertiary butylacetophenone in Preparation C yielded *p* - chloro - α - methylstyrene boiling at about 83—85°C. at 15 mm. pressure.

Substitution of an equimolecular amount of *p* - chloro - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine boiling at about 157—160°C. at 8 mm. pressure.

A mixture of 29.3 parts of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine, 15 parts of γ-chlorobutyrophenone, and 0.1 part of potassium iodide in 100 parts of toluene was heated for 70 hours at a temperature of 100—110°C. The contents of the flask were cooled and filtered. The solid residue was triturated with a mixture of 100 parts of ether and 100 parts of water. The ether layer was separated. To the filtrate from the original reaction mixture was added the ether layer. The solution was concentrated to induce the crystallisation of 1 - (γ - benzoylpropyl) - 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine. The solution was then cooled and the product collected on a filter. The white crystals melted at about 128—132.5°C.

EXAMPLE 4

Substitution of an equimolecular amount of p-bromoacetophenone for the *p* - tertiary - butylacetophenone in Preparation C yielded *p* - bromo - α - methylstyrene boiling at about 103—106°C. at 15 mm. pressure.

Substitution of an equimolecular amount of *p* - bromo - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*p* - bromophenyl) - 1,2,3,6 - tetrahydropyridine boiling at about 162°C. at 3 mm. pressure.

Substitution of 36 parts of 4 - (*p* - bromophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*p* - bromophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 211—214.5°C.

EXAMPLE 5

Substitution of an equimolecular amount of *p*-methylacetophenone for the *p* - tertiary - butylacetophenone in Preparation C yielded *p* - methyl - α - methylstyrene boiling at about 72—74°C. at 13 mm. pressure.

Substitution of an equimolecular amount of *p* - methyl - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine boiling at about 162—170°C. at 10 mm. pressure.

Substitution of 26.1 parts of 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 196.8—198°C.

EXAMPLE 6

Substitution of an equimolecular amount of p-ethylacetophenone for the *p* - tertiary - butylacetophenone in Preparation C yielded *p* - ethyl - α - methylstyrene boiling at about 60—61°C. at 6 mm. pressure.

Substitution of an equimolecular amount of *p* - ethyl - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*p* - ethylphenyl) - 1,2,3,6 - tetrahydropyridine boiling at about 150—164°C. at 8 mm. pressure.

Substitution of 28 parts of 4 - (*p* - ethylphenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*p* - ethylphenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 177.2—180.8°C.

EXAMPLE 7

Substitution of an equimolecular amount of *p* - tertiary - butyl - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*p* - tertiary butylphenyl) - 1,2,3,6 - tetrahydropyridine.

Substitution of 32.4 parts of 4 - (*p* - tertiary - butylphenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*p* - tertiary - butylphenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 231—237.5°C.

EXAMPLE 8

Substitution of an equimolecular amount of *o,p*-dimethylacetophenone for the *p* - tertiary - butylacetophenone in Preparation C yielded *o,p* - dimethyl - α - methylstyrene boiling at about 79—83°C. at 17 mm. pressure.

Substitution of an equimolecular amount of *o,p* - dimethyl - α - methylstyrene for the α-methylstyrene in Preparation D yielded 4 - (*o* - *p* - xylyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 216.8—220°C.

Substitution of 28.2 parts of 4 - (*o,p* - xylyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 1 yielded 1 - (γ - benzoylpropyl) - 4 - (*o,p* - xylyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 192.8—194.2°C.

EXAMPLE 9

A Grignard reagent was prepared from 6.7 parts of magnesium and 58 parts of *m*-bromofluorobenzene in 100 parts of ether. To this reagent was then added a solution of 26 parts of γ-chlorobutyronitrile in 80 parts of ether. After the addition was complete, the reaction mixture was refluxed and stirred for two hours. The mixture was then allowed to stand at room temperature for 15 hours. During the preceding operation, the mixture was kept under a nitrogen atmosphere. The excess Grignard reagent was decomposed by the addition of 56 parts of concentrated hydrochloric acid and 50 parts of water. The organic layer was separated, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure and the residue was distilled to yield γ - chloro - *m* - fluorobutyrophenone boiling at about 105—125°C. at 2 mm. pressure.

Substitution of 16.5 parts of γ - chloro - *m* - fluorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - *m* - fluorobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 193—194.8°C.

EXAMPLE 10

Substitution of 16.5 parts of γ - chloro - *p* - fluorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - fluorobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 186—187.4°C.

EXAMPLE 11

Substitution of 26.7 parts of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 10 yielded 1 - [γ - (*p* - fluorobenzoyl)propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 181.6—182.4°C.

EXAMPLE 12

Substitution of an equimolecular amount of *m*-bromochlorobenzene for the *m*-bromofluorobenzene in Example 9 yielded γ,*m*-dichlorobutyrophenone boiling at about 128—135°C. at 2mm. pressure.

Substitution of 17.8 parts of γ,*m*-dichlorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*m* - chlorobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 210—212°C.

EXAMPLE 13

Substitution of an equimolecular amount of chlorobenzene for the fluorobenzene in Preparation B yielded γ,*p*-dichlorobutyrophenone boiling at about 185—190°C. at 12 mm. pressure.

Substitution of 17.8 parts of γ,*p*-dichlorobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - chlorobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 213.5—216.5°C.

EXAMPLE 14

Substitution of an equimolecular amount of bromobenzene for fluorobenzene in Preparation B yielded γ - chloro - *p* - bromobutyrophenone boiling at about 150—157°C. at 6 mm. of pressure.

Substitution of 21.3 parts of γ - chloro - *p* - bromobutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - bromobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 227—28.5°C.

EXAMPLE 15

Substitution of an equimolecular amount of toluene for the fluorobenzene in Preparation B yielded γ - chloro - *p* - methylbutyrophenone boiling at 145°C. at 5 mm. pressure.

In a bomb a mixture of 26.7 parts of 4 - (*p* - fluorophenyl)) - 1,2,3,6 - tetrahydropyridine, 16.2 parts of γ - chloro - *p* - methylbutyrophenone, and 0.1 part of potassium iodide in 100 parts of toluene was heated for 72 hours at a temperature of 145—150°C. The contents of the bomb were cooled. The reaction mixture was filtered, and the remaining solid was triturated with 100 parts of water and 100 parts of ether. The ether layer was separated and added to the filtrate from the original reaction mixture. A portion of the ether was evaporated in order to induce crystallisation of the product. The precipitate thus obtained was collected on a filter and

recrystallised from a mixture of 2-propanol and acetone to yield 1 - [γ - (*p* - methylbenzoyl)propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine melting at about 125—126°C.

EXAMPLE 16

In an open flask a mixture of 16.2 parts of γ - chloro - *p* - methylbutyrophenone, 29.2 parts of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine, and 0.1 part of potassium iodide in 110 parts of toluene was heated for 50 hours at a temperature of 100—110°C. The contents of the flask were cooled and filtered. The filtrate was dried over anhydrous potassium carbonate. Anhydrous hydrogen chloride gas was passed through the solution, whereupon there precipitated the hydrochloride. The salt was collected on a filter and recrystallised from a mixture of 2-propanol and acetone to yield 1-[γ-(*p*-tolyl)-propyl] - 4 - (*p* - chlorophenyl) - 1,2,3,6-tetrahydropyridine hydrochloride melting at about 212.5—21.4°C.

EXAMPLE 17

Substitution of 26 parts of 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine for the 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine in Example 16 yielded 1 - [γ - (*p* - methylbenzoyl)propyl] - 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 212—215°C.

EXAMPLE 18

A mixture of 63 parts of γ-chlorobutyronitrile, 96 parts of 4 - phenyl - 1,2,3,6 - tetrahydropyridine, and 0.5 part of potassium iodide in 500 parts of toluene was heated at 100—110°C. for 70 hours. The mixture was cooled. The organic layer was separated, dried over anhydrous potassium carbonate, and filtered. Dry halogen chloride was passed through the solution. The precipitated salt was collected on a filter and recrystallised from a mixture of acetone and 2-propanol to yield γ - (4 - phenyl - 1,2,3,6 - tetrahydropyridine) - butyronitrile hydrochloride melting at about 191—192°C.

m - (Trifluoromethyl)phenylmagnesium bromide was prepared by adding a solution of 28.1 parts of *m*-bromotrifluoromethylbenzene in 80 parts of dry ether to 3.04 parts of magnesium turnings. After the addition was complete, stirring and refluxing was continued for 2 hours.

To 130 parts of this Grignard reagent was added with stirring a solution of 18.9 parts of γ - (4 - phenyl - 1,2,3,6 - tetrahydropyridine)butyronitrile in 40 parts of ether and 90 parts of benzene in the course of 30 minutes. Stirring and refluxing were continued for 5 hours The reaction mixture was permitted to stand at room temperature for 24 hours A solution of 25 parts of ammonium chloride in 75 parts of water was added, and the organic solvents were evaporated. The water lost during the evaporation was replaced. The mixture was refluxed for 1 hour, cooled, and extracted with ether. The ether extract was extracted with cold 2N hydrochloric acid. An oily layer formed, which soon solidified. The solid was collected by filtration. The ether layer was separated and discarded. The aqueous layer, together with the precipitate, was treated with sodium hydroxide solution. The free base was extracted with ether. The ether solution was dried over anhydrous potassium carbonate and dry, gaseous hydrogen chloride was passed through the solution, whereupon a finely divided precipitate was obtained. The ether was evaporated and the residue was purified by recrystallisation from a cooled mixture of acetone and 2-propanol in the presence of activated charcoal. In this manner there was thus obtained 1 - [γ - (*m* - trifluoromethylbenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 178.2—179.4°C.

EXAMPLE 19

Substitution of an equimolecular amount of *m*-xylene for the fluorobenzene in Preparation B yielded γ - chloro - 2,4 - dimethylbutyrophenone.

Substitution of 17.3 parts of γ - chloro - 2,4 - dimethylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 -[γ - (2^1,4^1 - dimethylbenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 197.6—199°C.

EXAMPLE 20

Substitution of an equimolecular amount of *p*-dimethylbenzene for the fluorobenzene in Preparation B yielded γ - chloro - 2,5 - dimethylbutyrophenone boiling at about 142—148°C. at 6 mm. pressure.

Substitution of 17.3 parts of γ - chloro - 2,5 - dimethylbutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (2^1,5^1 - dimethylbenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 174—177°C.

EXAMPLE 21

Substitution of 29.3 parts of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 19 yielded 1 - [γ - (2^1,4^1 - dimethylbenzoyl)propyl] - 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 214—216°C.

EXAMPLE 22

A mixture of 94 parts of phenol and 142 parts of γ-chlorobutyryl chloride was refluxed for 3 hours. The mixture was then fractionated *in vacuo* to yield the phenol ester of γ-chlorobutyric acid boiling at about 140—143°C. at 10 mm. pressure.

To a solution of 77 parts of aluminium chloride in 760 parts of nitrobenzene were added slowly under stirring 100 parts of the phenol ester of γ-chlorobutyric acid. After the addition was completed, the stirring was continued for 18 hours at room temperature. The

reaction mixture was then poured into a mixture of 240 parts of concentrated hydrochloric acid and 400 parts of ice. The solution was filtered. The remaining solid was taken up in 142 parts of ether. The residual water was separated, and the solution was diluted with 50 parts of petroleum ether. The solution was cooled and scratched. The γ - chloro - *p* - hydroxybutyrophenone was collected on a filter and found to melt at about 114—115.2°C.

Substitution of 16.3 parts of γ - chloro - *p* - hydroxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - hydroxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 271—272.5°C.

EXAMPLE 23

Substitution of an equimolecular amount of anisole for the fluorobenzene in Preparation B yielded γ - chloro - *p* - methoxybutyrophenone boiling at 175°C. at 6 mm. pressure.

In a sealed reactor a mixture of 24 parts of 4 - phenyl - 1,2,3,6 - tetrahydropyridine, 17.5 parts of γ - chloro - *p* - methoxybutyrophenone, and 0.1 part of potassium iodide in 100 parts of toluene was heated for 50 hours at a temperature of 120—125°C. After cooling, the reaction mixture was filtered. The filtrate was concentrated and then cooled. The precipitate thus obtained was collected on a filter and recrystallised from a mixture of 2-propanol and acetone to yield 1 - [γ - (*p* - anisoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine melting at about 122.2—123.4°C.

This base was dissolved in ether. Dry, gaseous hydrogen chloride was passed through the solution, whereupon there precipitated the hydrochloride. The salt was collected on a filter and recrystallised from a mixture of 2-propanol and acetone to yield 1 - [γ - (*p* - anisoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 202.5—204°C.

EXAMPLE 24

Substitution of 26.7 parts of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 23 yielded 1 - [γ - (*p* - anisoyl)propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine melting at about 117.8—120°C.

EXAMPLE 25

Substitution of 29.3 parts of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine in Example 23 yielded 1 - [γ - (*p* - anisoyl)-propyl] - 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine melting at about 138—139°C.

EXAMPLE 26

Substitution of 26.1 parts of 4 - (*p* - methylphenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 23 yielded 1 - [γ - (*p* - anisoyl) - propyl] - 4 - (*p* - tolyl) - 1,2,3, 6- tetrahydropyridine melting at about 127—128.5°C.

EXAMPLE 27

Substitution of an equimolecular amount of phenetole for the fluorobenzene in Preparation B yielded γ - chloro - *p* - ethoxybutyrophenone melting at about 50.4—51.8°C.

Substitution of 18.6 parts of γ - chloro - *p* - ethoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - ethoxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 174.2—176°C.

EXAMPLE 28

Substitution of an equimolecular amount of propoxybenzene for the fluorobenzene in Preparation B yielded γ - chloro - *p* - propoxybutyrophenone boiling at 183°C. at 6 mm. pressure.

Substitution of 19.7 parts of γ - chloro - *p* - propoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*p* - propoxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 175—176.2°C.

EXAMPLE 29

Substitution of an equimolecular amount of butyl phenyl ether for the fluorobenzene in Preparation B yielded γ - chloro - *p* - butoxybutyrophenone melting at 36.8—38°C.

Substitution of 20.9 parts of γ - chloro - *p* - butoxybutyrophenone for the γ - chloro-*p* - methoxybutyrophenone in Example 23 yielded 1 - [γ - (p - butoxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine melting at about 111.2—112.2°C.

EXAMPLE 30

Substitution of an equimolecular amount of *o*-dimethoxybenzene for the fluorobenzene in Preparation B yielded γ - chloro - *m,p* - dimethoxybutyrophenone melting at about 92—93°C.

Substitution of 19.9 parts of γ - chloro - *m,p* - dimethoxybutyrophenone for the γ-chlorobutyrophenone in Example 1 yielded 1 - [γ - (*m,p* - dimethoxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 198—199°C.

EXAMPLE 31

A mixture of 84 parts of thiophene, 141 parts of γ-chlorobutyryl chloride, and 870 parts of benzene is cooled to about 0°C. While this temperature was maintained, 260 parts of stannic chloride were added over a two hour period. After the addition was completed, the cooling bath was removed and the stirring was continued for about an hour. The reaction mixture was then poured into a mixture of 60 parts of concentrated hydrochloric acid and 450 parts of ice water. The organic layer was separated, washed with water, dried over anhydrous calcium chloride, and filtered. The filtrate was concentrated under reduced pressure. The residue was distilled to yield 2 - (γ - chlorobutyryl)thio-

phene which boiled at 144—146°C. at 11 mm. of pressure.

In an open flask a mixture of 15.5 parts of 2 - (γ - chlorobutyryl)thiophene, 24 parts of 4 - phenyl - 1,2,3,6 - tetrahydropyridine, and 0.1 part of toluene was heated under reflux for about 70 hours. The contents of the flask were cooled and then filtered. The solid residue was triturated with a mixture of 100 parts of water and 100 parts of ether. The ether layer was separated and added to the filtrate from the original reaction mixture. The combined solution was dried over anhydrous potassium carbonate and filtered. Dry, gaseous hydrogen chloride was introduced into the solution. The precipitated salt was collected on a filter and recrystallised from a mixture of 2-propanol and acetone to yield the hydrochloride of 1 -[γ - (2 - thenoyl)-propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine melting at about 200.4—202.6°C.

Substitution of an equimolecular amount of β - methyl - γ - chlorobutyryl chloride for the γ-chlorobutryl chloride yielded the colourless needles of 2 - (β - methyl - γ - chlorobutyryl)thiophene.

Substitution of 16.7 parts of 2 - (β - methyl - γ - chlorobutyryl)thiophene for the 2 - (γ - chlorobutyryl)-thiophene in the preceding procedure yielded the white, prismatic crystals of 1 - [β - methyl - γ - (2 - thenoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride.

EXAMPLE 32

Substitution of 26.7 parts of 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine in Example 31 yielded 1 - [γ - (2 - thenoyl)-propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at 178—180.5°C.

EXAMPLE 33

Substitution of 29.3 parts of 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 31 yielded 1 - [γ - (2 - thenoyl)-propyl] - 4 - (*p* - chlorophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at about 207—208.5°C.

EXAMPLE 34

Substitution of 26.1 parts of 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 31 yielded 1 - [γ - (2 - thenoyl(propyl] - 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at 200—203°C.

EXAMPLE 35

Substitution of 28.2 parts of 4 - (*o,p* - xylyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 31 yielded 1 - [γ - (2 - thenoyl)-propyl] - 4 - (*o,p* - xylyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at 163—163.6°C.

EXAMPLE 36

Substitution of 36 parts of 4 - (*p* - bromophenyl) - 1,2,3,6 - tetrahydropyridine for the 4 - phenyl - 1,2,3,6 - tetrahydropyridine in Example 31 yielded 1 - [γ - (2 - thenoyl)-propyl] - 4 - (*p* - bromophenyl) - 1,2,3,6 - tetrahydropyridine hydrochloride melting at 218—220°C.

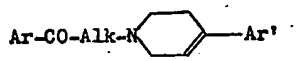
EXAMPLE 37

Substitution of an equimolecular amount of δ-chlorovaleryl chloride for the γ-chlorobutyryl chloride in Example 31 yielded 2 - (δ - chlorovaleryl)thiophene.

Substitution of 16.5 parts of 2 - (δ - chlorovaleryl)thiophene for the 2 - (γ - chlorobutyryl)thiophene in Example 31 yielded the colourless needles of 1 - [δ - (2 - thenoyl)-butyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine hydrochloride.

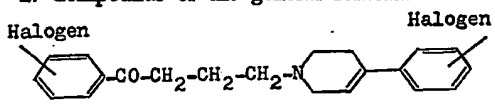
WHAT I CLAIM IS:—

1. Compounds of the general formula



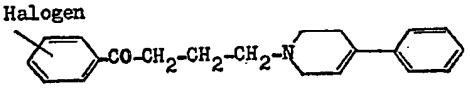
and their pharmaceutically acceptable salts wherein Ar and Ar^1 are each a halophenyl radical, an alkoxyphenyl radical containing less than eleven carbon atoms or a dimethoxyphenyl, hydroxyphenyl, thienyl, trifluoromethylphenyl or monocyclic aromatic hydrocarbon radical containing less than 11 carbon atoms, and wherein Alk is an alkylene radical containing from three to six carbon atoms.

2. Compounds of the general formula



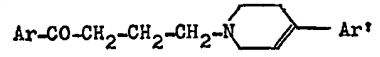
3. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine.

4. Compounds of the general formula



5. 1 - [γ - (*p* - Fluorobenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

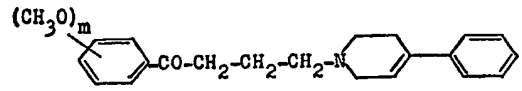
6. Compounds of the general formula



and their pharmaceutically acceptable salts wherein Ar and Ar^1 are each aromatic hydrocarbon radicals containing less than 11 carbon atoms.

7. 1 - (γ - Benzoylpropyl) - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

8. Compounds of the general formula



and their pharmaceutically acceptable salts

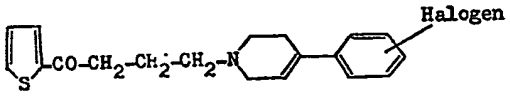
wherein m is a positive integer less than 3.

9. 1 - [γ - (*p* - Methoxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

10. 1 - [γ - (*m,p* - Dimethoxybenzoyl)-propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

11. 1 - [γ - (*p* - Hydroxybenzoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

12. Compounds of the general formula



and their pharmaceutically acceptable salts.

13. 1 - [γ - (2 - Thenoyl)propyl] - 4 - (*p* - fluorophenyl) - 1,2,3,6 - tetrahydropyridine.

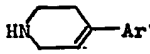
14. 1 - [γ - (2 - Thenoyl)propyl] - 4 - (*p* - tolyl) - 1,2,3,6 - tetrahydropyridine.

15. 1 - [γ - (2 - Thenoyl)propyl] - 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

16. A process for the preparation of the compounds claimed in any one of the preceding claims which comprises condensing an aroylalkyl halide of the general formula

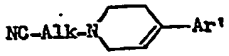
Ar—CO—Alk—Halogen

with at least one equivalent of a compound of the general formula



wherein Ar and Ar^1 have the meanings given in claim 1.

17. A process for the preparation of the compounds claimed in any one of the preceding claims 1 to 15 which comprises reacting ω - (4 - aryl - 1,2,3,6 - tetrahydropyridine)-alkanonitrile of the general formula



with an aryl magnesium halide of the general formula

Ar—Mg—Halogen

where Ar and Ar^1 have the meanings given in claim 1, decomposing the complex formed and recovering the product.

18. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any of Examples 1 to 8, 10, 13, 14, 20 and 31 to 36.

19. A process for the preparation of the compounds claimed in claim 1 substantially as described with reference to any one of Examples 9, 11, 12, 15 to 19, 21 to 30 and 37.

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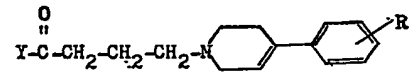
PROVISIONAL SPECIFICATION

Tetrahydropyridine Derivatives

I, PAUL ADRIAAN JAN JANSSEN, of Antwerpse Steenweg 16[1], Vosselaar near Turnhout, Belgium, A Citizen of Belgium, do hereby declare this invention to be described in the following statement:—

This invention relates to tetrahydropyridine derivatives.

The novel compounds of this invention are 1 - aroyl - propyl - 4 - aryl - 1,2,3,6 - tetrahydropyridine derivatives of the general structural formula:



and therapeutically useful salts thereof wherein Y is a phenyl, alkyl-substituted phenyl, halogenated phenyl, alkoxyphenyl or thienyl radical and R is hydrogen, an alkyl radical or a halogen atom.

The compounds of the invention can be prepared by condensing an appropriately selected aroylpropyl halide with the desired 4 - aryl - 1,2,3,6 - tetrahydropyridine. The reaction can be carried out in an inert solvent such as benzene, toluene, ethanol, butanol, dioxane and methyl isobutyl ketone at elevated temperatures and pressures.

Alternatively, the compounds of the invention can be made by reacting 4 - phenyl - 1,2,3,6 - tetrahydropyridinobutyronitrile or an appropriately substituted phenyl derivative thereof with an aryl magnesium halide, decomposing the resulting complex and recovering the product. The 4 - phenyl - 1,2,3,6 - tetrahydropyridinobutyronitriles required for this synthesis can be prepared by condensing γ-chlorobnutyronitrile with 4 - phenyl - 1,2,3,6 - tetrahydropyridine.

Suitable aroylpropyl halides for use as intermediates for the preparation of compounds of the invention, are, for example, γ-halobutyrophenones such as γ-chlorobutyrophenone, γ-bromobutyrophenone, and nuclearly substituted derivatives thereof in which the nuclear substituents are for example, halogen atoms of alkyl or alkoxy radicals. These intermediates can be prepared conveniently by the Friedel-Crafts reaction including its milder variations, employing, for example, γ-chlorobutyryl chloride and benzene or an appropriately substituted benzene such as toluene or *m*-xylene, a halogenated benzene such as chlorobenzene, bromobenzene or fluorobenzene or an alkoxybenzene such as anisole or phenetol.

Alternatively, these intermediates can be prepared by treating γ-chlorobutyronitrile with the desired aryl-magnesium bromide followed by acid hydrolysis.

Suitable 4 - aryl - 1,2,3,6 - tetrahydropyridines can be prepared according to the method of Schmidle by the condensation of α - methyl - styrene, or an appropriately nuclearly substituted derivative thereof, with ammonia and formaldehyde to produce the corresponding 6 - methyl - 6 - aryltetrahydro - 1,3 - oxazine followed by acid hydrolysis to yield the desired 4 - aryl - 1,2,3,6 - tetrahydropyridine.

The compounds of the invention have useful pharmacological properties. They are potent depressants of the central nervous system and exhibit marked transquilising effects in low dosage.

The invention is illustrated in greater detail in the following examples. Temperatures are expressed in degrees Centigrade (°C.). Quantities are expressed in parts by weight and parts by volume which bear the same relation one to the other as kilograms to litres.

PREPARATION A

Benzoylpropyl chloride

A solution of 71 parts by weight of γ-chlorobutyryl chloride in 71 parts by volume of anhydrous benzene was added with stirring to a suspension of 71 parts by weight of anhydrous aluminium chloride in 355 parts by volume of anhydrous benzene maintained at 10—15°. After the addition was complete, the cooling bath was removed and stirring continued for an additional 30 minutes. The reaction mixture was poured into ice water, the benzene layer separated, dried over anhydrous sodium sulphate and filtered. The filtrate was concentrated under reduced pressure to remove the benzene and the residue distilled to yield γ-chlorobutyrophenone which boiled at 134—137° at 5 millimetres pressure.

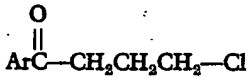
By using equivalent quantities of toluene instead of benzene and otherwise proceeding as described above 4-methylbenzoylpropyl chloride was obtained which boiled at 100—110° at 4 millimetres pressure.

PREPARATION B

4-Fluorobenzoylpropyl chloride

To a suspension of 341 parts by weight of aluminium chloride in 1375 parts by volume of anhydrous carbon disulphide was added 96 parts by weight of fluorobenzene while stirring and maintaining at 10—15°. Then 141 parts by weight of γ-chlorobutyryl chloride was added slowly while maintaining the temperature at 10°. After the addition was complete the cooling bath was removed and the stirring was continued for about one hour until no more hydrogen chloride was evolved.

Using equivalent quantities of appropriately substituted benzenes and otherwise proceeding as above the following aroylpropyl chlorides were obtained:



Ar	b.p. (m.p.)
4—ClC_6H_4	135—140°/8 mm
4—BrC_6H_4	150—157°/6.5 mm
4—$CH_3OC_6H_4$	175°/6 mm
2,4-$(CH_3)_2C_6H_3$	130—143°/1 mm
2,5-$(CH_3)_2C_6H_3$	142—145°/6 mm
2,5-$(CH_3O)_2C_6H_3$	150—190°/4 mm (27—30°)

For the 2,4-dimethyl- and 2,5-dimethyl derivatives the reaction mixture was heated for about half an hour prior to the decomposition with ice water. For subsequent processing according to the synthesis disclosed herein it is not essential that the aroylpropyl chloride be analytically pure.

PREPARATION C

2-Thenoylpropyl chloride

A mixture of 84 parts by weight of anhydrous thiophene, 141 parts by weight of γ-chlorobutyryl chloride and 1000 parts by volume of anhydrous benzene was cooled to 0 to −5°. While maintaining this temperature, 260 parts by weight of stannic chloride was added slowly over a two hour period. After the addition was complete, the cooling bath was removed and the stirring continued for about a further hour. The reaction mixture was then poured into a mixture of 50 parts by volume of concentrated hydrochloric acid and 450 parts by volume of ice water.

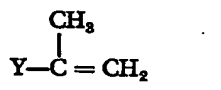
The organic layer was separated, washed with water, dried on calcium chloride and filtered. The filtrate was concentrated under reduced pressure and the residue distilled to yield 3 - (2 - thienoyl)propyl chloride which boiled at 144—146° at 11 millimetres pressure.

PREPARATION D

4-tertiary-Butyl-α-methyl styrene

A solution of 95 parts by weight of ice cold methylbromide in 500 parts by volume of anhydrous ether was added dropwise to a refluxing suspension of 24 parts by weight of magnesium in 300 parts by volume of ether. The mixture was refluxed for an additional 2 hours and then 117.5 parts by weight of *p*-tertiary butylacetophenone was added in the course of 90 minutes. The refluxing was continued for an additional 3 hours and then the mixture was stirred overnight at room temperature. The Grignard complex was destroyed by the addition of ammonium chloride and 10% hydrochloric acid. The mixture was extracted with ether, the ether extracts washed with 10% sulphuric acid, then with water and dried over anhydrous calcium chloride. The solution was filtered and concentrated *in vacuo* to remove the solvents. About 0.5 parts by weight of hydroquinone was added to the residue which was then heated to a temperature of about 100—110° under a pressure of about 50 millimetres. The distillate consisting of a mixture of water and 4 - tertiary - butyl - α - methylstyrene was extracted with ether and the other extracts dried over anhydrous calcium chloride. The mixture was separated by filtration, a small quantity of hydroquinone added to the ether solution which was fractionated by distillation to yield 4 - tertiary - butyl - α - methylstyrene which boiled at about 98° at 5 millimetres pressure.

Using appropriately substituted acetophenone and otherwise proceeding as described above the following correspondingly substituted α-methylstyrenes were obtained:



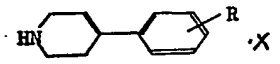
Y	b.p.	pressure	UV λ	UV Σ
3-fluorophenyl	82—84°	50 mm	243.7	8720
4-ethylphenyl	60—61°	6	249.5	11,500
2,4-dimethylphenyl	79—83°	17	278	342
2,5-dimethylphenyl	102—105°	30	278	466

PREPARATION E

4-Aryl-1,2,3,6-tetrahydropyridine

A mixture of 856 parts by weight of ammonium chloride and 3000 parts by weight of 36% formaldehyde solution was stirred and heated to 60°. At this temperature 944 parts by weight of α-methylstyrene was added slowly with cooling to maintain the temperature. After the addition was complete, the mixture was stirred at room temperature until the temperature of the reaction mixture dropped to 40°. After adding 2000 parts by volume of methanol, the stirring was continued for about 20 hours, then the methanol was removed *in vacuo* and the residue diluted with 2500 parts by volume of concentrated hydrochloric acid. The mixture was heated with stirring to a temperature of about 100° for 4 hours, cooled, diluted with 2000 parts by volume of water and made alkaline by the addition of 15 Normal sodium hydroxide solution. The reaction mixture was extracted with benzene, the benzene extracts dried over anhydrous potassium carbonate, filtered and the benzene removed from the filtrate. The residue remaining was distilled *in vacuo* to yield 4 - phenyl - 1,2,3,6 - tetrahydropyridine which boiled at 97—112° at 1 millimetre pressure. Its hydrochloride melted at 199—202°.

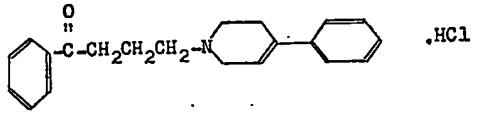
By substituting equivalent quantities of appropriately substituted α-methylstyrene derivatives for the α-methylstyrene used above and otherwise proceeding as described above the following correspondingly substituted 4 - phenyl - 1,2,3,6 - tetrahydropyridines were obtained:



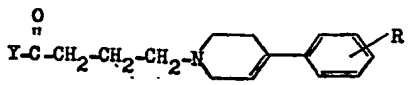
R	X	Melting Point	Melting Point
H	base		—
H	HCl	199—202	
4—CH_3	base		b_{10} = 162—170
4—CH_3	HCl	192.4—194	
4—C_2H_5	base	—	b_8 = 150—164
4—C_2H_5	HCl	177.5—179	
2,4—$(CH_3)_2$	HCl	216.8—220	
4—F	base		$b_{4-4.5}$ = 139—141
4—Cl	base	62—63	b_8 = 157—160
4—Cl	HCl	192—194.2	
3—Br	HCl	261—267	
4—Br	HCl	243.5—245	
3—F	base	—	b_8 = 144—145
4-tertiary-butyl	base		b_3 = 150—155
4-tertiary-butyl	HCl	193.5—207	
4—Br	base	35—35.5	b_3 = 162°

EXAMPLES

A mixture of 15 parts by weight of γ-chlorobutyrophenone, 24 parts by weight of 4 - phenyl - 1,2,3,6 - tetrahydropyrimidine, 0.1 part by weight of potassium iodide and 100 parts by volume of toluene was heated in a pressure vessel at about 145—150° for about 72 hours. After cooling, the reaction mixture was filtered and the solid residue agitated with a mixture of 100 parts by volume of water and 100 parts by volume of ether. The ethereal layer was separated and added to the filtrate from the original reaction mixture and the combined solutions dried over potassium carbonate. After separating from the drying agent, a stream of dry gaseous hydrogen chloride was passed through the solution. The solid thus precipitated was recovered and crystallised from a mixture of isopropanol and acetone (3:2) to yield the hydrochloride of γ - (4 - phenyl - 1,2,3,6 - tetrahydropyridino) - butyrophenone which melted at 195—196.2° and had the formula:



Using equivalent quantities of appropriately substituted starting materials and otherwise proceeding as described above, the compounds listed below were obtained:



Y	R	X	Melting Point
C_6H_5	H	HCl	195—196.2
C_6H_5	4—CH_3	HCl	196.8—198
C_6H_5	2,4—$(CH_3)_2$	HCl	192.8—194.2
C_6H_5	4—C_2H_5	HCl	177.2—180.8
C_6H_5	4-tertiarybutyl	HCl	231—237.5
C_6H_5	4—F	HCl	182.6—183.6
C_6H_5	4—Cl	base	128—132.5
C_6H_5	4—Br	HCl	211—214.5
2,4—$(CH_3)_2$—C_6H_3	H	HCl	174—177
4—F—C_6H_4	H	HCl	186—187.4
2-thienyl	H	HCl	200.4—202.6
2-thienyl	4—CH_3	HCl	200—203
2-thienyl	2,4—$(CH_3)_2$	HCl	163—163.6
2-thienyl	4—F	HCl	178—180.5
2-thienyl	4—Cl	HCl	207—208.5
4—Br—C_6H_4	H	HCl	227—228.5
2-thienyl	4—Br	HCl	218—220
4—Cl—C_6H_4	H	HCl	213.5—216.5
4—CH_3O—C_6H_4	H	HCl	202.5—204
2,4—$(CH_3)_2$—C_6H_3	H	HCl	197.6—199

For the purpose of this invention therapeutically useful salts are equivalent to the free bases. Among such suitable therapeutically useful salts are the hydrohalides, for example, the hydrochloride and the hydrobromide, sulphate, citrate, malate, maleate, ascorbate, tartrate, acetate and benzoate.

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